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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,945	05/02/2001	Neil P. Desai	ABI1460-3 (071243-1317)	6174

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EXAMINER	
GOLLAMUDI, SHARMILA S	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 07/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,945	DESAI ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-18 and 20-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-18 and 20-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt for Request for Continued Examination and Amendments filed June 3, 2005 is acknowledged. Claims **1, 3-18, and 20-30** are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-18, and 20-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendment of 6/3/05 recites a "non-cancerous cells", which is not supported by the instant specification. It should be further noted that applicant has not cited any specific pages or lines where support may be found in the instant specification. It should be noted that MPEP 2163.06 requires the applicant point out support for amendments made to the claims. If applicant contends there is support, the specific page and line in which support can be found is requested.

The amendment of 9/14/04 recites an "amorphous drug", which is not supported by the instant specification. It should be further noted that applicant has not cited any specific pages or lines where support may be found in the instant specification. If applicant contends there is support, the specific page and line in which support can be found is requested.

Response to Arguments

Applicant asserts that the instant specification incorporates US 98/13272 in its entirety and the phrase amorphous is supported in US 98/13272.

Applicant's arguments filed 6/3/05 have been fully considered, however the examiner requests a copy of US 98/13272's specification, which is unavailable at this time, to determine support. Once support is determined, the rejection with regard to "amorphous" will be withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 18, 20-28, and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Desai et al (5,916, 596).

Desai et al discloses an anticancer drug, specifically paclitaxel, coated with a protein for the treatment of cancer. Note that cancer is a type of hyperplasia. See abstract. The invention provides for small nanoparticles that are delivered in-vivo. See column 5, lines 53-55 and column 8, lines 17-22. Example 18 discloses intravenous therapy. The drug may be in a crystalline form or amorphous with amorphous preferred since it increases bioavailability. See column 7, lines 1-5 and claim 25. Example 14 discloses the treatment of tumors in an animal

model by administering paclitaxel nanoparticles in tumor bearing mice. Lastly, example 30 discloses the reduced toxicity of the inventive protein coated drug nanoparticles.

Response to Arguments

Applicant argues that the instant claims are distinguished over the prior art since the instant invention is directed to a **composition** for treating hyperplasia of non-cancerous cells in the blood vessel.

Applicant's arguments filed 6/3/05 have been fully considered but they are not persuasive. Firstly, it should be noted that the claims that are rejected are directed to a composition and the rejection over the method claims have been withdrawn in view of the amendments of 6/3/05. The examiner points out that the a recitation of the intended use of a product (composition) must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 370 F.2d 576, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 312 F.2d 937, 939, 136 USPQ 458, 459 (CCPA 1963). In instant case, independent claims 25 and 30 are directed to a composition comprising a drug selected from an antiproliferative, an angiogenesis inhibitor, or mixture thereof, in a nanoparticle form which is coated with a protein. Independent claim 18 is directed to a composition comprising a drug selected from an antiproliferative, an angiogenesis inhibitor, or mixture thereof, in a nanoparticle form and a protein. The examiner points out that Desai discloses an anticancer drug nanoparticle, specifically paclitaxel, coated with a protein. Therefore, the instantly claimed composition and

the prior art are not structurally different and thus the prior art is capable of performing the intended use.

Accordingly, Desai et al is said to anticipate the composition claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3-18, and 20-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kunz et al (5,733,925) of Westesen et al (6,197,349).

Kunz et al disclose methods for inhibiting stenosis following vascular trauma or disease, cancer, diseases resulting from hyperactivity or hyperplasia of somatic cells. Example 7 discloses smooth muscle proliferation in the neointima. Kunz teaches direct or targeted delivery of therapeutic agents to vascular smooth muscle cells. See column 1, lines 15-35. Inhibiting stenosis following angioplasty is contemplated. See column 3, lines 54-62. The dosage forms are preferably in biodegradable microparticulates or nanoparticulates wherein the particles are

formed of a polymer-containing matrix that biodegrades. Kunz et al teach conjugating the drug with a binding protein to target the cells and reduce toxicity. Example 7 notes the toxicity of a free drug versus a conjugated drug. See column 14, lines 25-33. Kunz et al disclose that the direct sustained release dosage form-binding protein or peptide conjugations may disrupt binding protein/peptide target cell recognition. Therefore, ligand sandwich attachment techniques are utilized. Such a technique involves the formation of a primary peptide or *protein shell* using a protein that does not bind to the target cell population. The binding protein/peptide is then bound to the primary peptide or protein shell to provide a particulate with functional binding protein/peptide. For example, the poly-lactic/glycolic acid particulates are reacted with avidin or streptavidin to form *protein-coated particulates*. Additionally, the binding protein/peptide may be partially entrapped in the particulate polymeric matrix upon formation of the particulate. See column 25, line 20 to column 26, line 40. Therapeutic agents such as taxol or analogs are preferred therapeutic agents that are designed to target the cell activity without killing the cell. Taxol is taken into the cell and stabilizes the cell from further dividing. See column 4, lines 40-45 and column 13, lines 24-27. Examples of dosages include .01 to 10 mg/kg per day. For prevention of restenosis following angioplasty or an intervention that contributes to the acute proliferation of smooth muscle cells, a pre-loading dose is given prior to or at the time of intervention with smaller chronic doses given two or three weeks after intervention. For example, a single dose may be administered about 24 hours prior to intervention, while multiple preloading doses may be administered daily for several days prior to intervention. See column 29, lines 10-15. Delivery of the active agents may be intravenous, intra-arterial (stents), or local delivery. See column 30, lines 56-65 and examples for stent deployment.

Kunz et al do not specify the drug form, i.e. instant amorphous form.

Westesen et al teach nanoparticles containing various poorly water-soluble drugs. See abstract. Westesen teaches the use of an amorphous form of the drug to provide for better solubility and bioavailability of poorly water-soluble drugs than utilizing a crystalline form. See column 5, lines 45-56. Generally amorphous forms of a substance exhibit a higher solubility and a faster dissolution than the crystals forms since they do not require lattice energy.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an amorphous drug form in Kunz et al's nanoparticles. One would have been motivated to do so since Westesen teaches the use of an amorphous form for better solubility and bioavailability of poorly water-soluble drugs. Moreover, one would reasonably expect success by applying Westesen's teachings to Kunz since both are directed to poorly water-insoluble drugs.

Response to Arguments

Applicant argues that the instant claims are directed to an amorphous drug in a nanoparticle coated with a protein. Applicant argues that Kunz contemplates conjugating the drug with a binding protein and does not disclose a protein-coated nanoparticle. Applicant argues that Westesen is directed to particles that are a supercooled melt of poorly soluble substances and supercooled particles are very different from those discloses in Kunz and the instant invention. Applicant argues that Westesen teaches elevated temperatures that are not compatible with delicate protein structures.

Applicant's arguments filed 6/3/05 have been fully considered but they are not persuasive. It should be noted that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,

440 F.2d 442, 169 USPQ 423 (CCPA 1971). As pointed out in the Final Office Action of 12/6/04, on column 25 and 26 Kunz teaches different methods of making the micro and nanoparticulates. The examiner particularly points to column 26, line 2 wherein "protein coated particulates" are taught. The claims are rejected under obviousness and Kunz clearly suggest the use of a particulate coated with a protein such as avidin.

With regard to Westesen, the examiner points out that the *only* teaching lacking in Kunz et al is the teaching of an amorphous type of drug. It should be further noted that Kunz is not deficient in any other teaching. Therefore, the examiner relies on Westesen to cure this deficiency and provide a skilled artisan with the motivation for utilizing amorphous forms of drugs. Westesen clearly teaches that to provide improved bioavailability of a poorly water-soluble drug, the amorphous states have a higher rate of dissolution and solubility. A skilled artisan would have reasonably expected success by utilizing an amorphous form of Kunz's taxol since taxol is a water-insoluble drug. Westesen is not utilized in the formation of the particles since Kunz is not deficient in this sense and thus Westesen's use of high temperature levels is moot.

Accordingly, the rejection is maintained.

Claims 1, 3-17, and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al (5,916, 596) in view of Kinsella et al (5,616,608) or vice-versa wherein claims 1, 3-18, and 20-30 are rejected over Kinsella et al in view of Desai et al.

Desai et al discloses an anticancer (antineoplastic) drug, specifically paclitaxel (taxol), coated with a protein for the treatment of cancer. Note that cancer is a type of hyperplasia. See abstract. Taxol exhibits a unique mode of action on microtubule proteins responsible for the

formation of the mitotic spindle. See column 2, lines 48-50. The invention provides for small nanoparticles that are delivered in-vivo. See column 5, lines 53-55 and column 8, lines 17-22. Desai teaches the use of intravenous administration to deliver the nanoparticles and the nanoparticles are advantageous in targeting specific sites in the body. See examples 16-18. Various drugs may be utilized for various treatments. The drug may be in a crystalline form or amorphous with amorphous preferred since it increases bioavailability and has increased dissolution. See column 7, lines 1-5 and claim 25. Example 14 discloses the treatment of tumors in an animal model by administering paclitaxel nanoparticles in tumor bearing mice. Lastly, example 21 discloses the reduced toxicity of the inventive protein coated drug nanoparticles.

Desai does not teach the instant methodology of treating non-cancerous cell proliferation in blood vessels.

Kinsella teaches a method of treating atherosclerosis or restenosis using microtubule stabilizing agent such as taxol or taxol derivatives. IT=t should be noted that restenosis is the excessive proliferation of smooth muscle cells, I.e. non-cancerous cells, in the blood vessel. During angioplasty, intraarterial balloon catheter inflation results in deendothelialization, disruption of the internal elastic lamina, and injury to medial smooth muscle cells. While restenosis likely results from the interdependent actions of the ensuing inflammation, thrombosis, and smooth muscle cell accumulation (Ferrell, M., et al. (1992) Circ., 85:1630-1631), the final common pathway evolves as a result of medial VSMC dedifferentiation from a contractile to a secretory phenotype. This involves, principally, VSMC secretion of matrix metalloproteinases degrading the surrounding basement membrane, proliferation and chemotactic migration into the intima, and secretion of a large extracellular matrix, forming the

neointimal fibropoliferative lesion. Much of the VSMC phenotypic dedifferentiation after arterial injury mimics that of neoplastic cells (i.e., abnormal proliferation, growth-regulatory molecule and protease secretion, migration and basement invasion). See column 3, lines 30-46. Kinsella discloses that taxol is an antimicrotubule agent that promotes the formation of usually stable microtubules inhibiting the normal dynamic reorganization of the microtubule network required for mitosis and cell proliferation. See column 2, lines 50-60. Kinsella teaches the use of 2mg/kg taxol solution reduces the neointima area. See example 5. Kinsella teaches the use of local sustained delivery provide the best solution to prevent restenosis post-angioplasty and essentially eliminate problems of systemic toxicity. See column 11, lines 10-30. The dosing schedule can consist of a 24 hour continuous IV pretreatment in an amount of 0.5-2 mg/kg, 0.25-2 mg/kg continuous IV post-procedure, then about 0.25-2 mg/kg continuous infusion over 24 hours every 21 days for 1 to 6 cycles. See column 5, lines 40-56.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to utilize Desai's protein coated drug (antineoplastic drug taxol) for the treatment of proliferation of non-cancerous cells in blood vessels (restenosis). One would have been motivated to do so since Kinsella teaches the use of taxol to reduce atherosclerosis or restenosis since taxol promotes the formation of usually stable microtubules inhibiting the normal dynamic reorganization of the microtubule network required for mitosis and cell proliferation. Furthermore, Desai et al also recognize taxol's unique mode of action on microtubule proteins responsible for the formation of the mitotic spindle. Therefore, one would have expected success by utilizing Desai's taxol to treat abnormal proliferation in the blood vessels since Kinsella teaches taxol is an effective drug that prevents or reduces cell proliferation in the blood vessels.

Conversely, it would have been obvious for one of ordinary skill in the art at the time the invention was made to utilize Desai's protein coated taxol in Kinsella's methodology of treating proliferation of cells in blood vessels. One would have been motivated to do so with the expectation of success since Desai teaches coating taxol with a protein reduces systemic toxicity and may be utilized for targeting specific site in the body and Kinsella teaches the use of taxol in a local sustained delivery system offer the best solution for treating restenosis and eliminating systemic toxicity.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 18, 20-28, and 30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 4-6, 13-14, and 17 of U.S. Patent No. 6749868. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant claims 25 and 30 are directed to a composition comprising a drug selected from an antiproliferative, an antineoplastic drug, an angiogenesis inhibitor, or mixture thereof, in a nanoparticle form which is coated with a protein. Independent claim 18 is directed to a

composition comprising a drug selected from an antiproliferative, an antineoplastic drug, an angiogenesis inhibitor, or mixture thereof, in a nanoparticle form and a protein.

US patent '868 is directed to a drug delivery system comprising particles of a substantially water-insoluble drug, which is coated with a protein wherein the diameter of the particles are no greater than 1 micron. Claim 2 is directed to particles of less than 200 nm. Claim 5 is directed to amorphous particles. Claim 14 is directed to an anti-neoplastic drug taxol.

The instant application and US patent are directed to similar and overlapping subject matter. It should be noted that the intended use (a composition for the treatment of hyperplasia) of the instant invention is not given patentable weight since it merely recites the purpose of the composition and does not provide a structural limitation. Furthermore, it should be noted that the instant preamble directed to "a composition" and the US patent's preamble "a drug delivery system" are both product claims.

Claims 18 and 20-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-25 of U.S. Patent No. 6096331 in view of Westesen et al (6,197,349). Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Independent claim 18 is directed to a composition comprising a drug selected from an antiproliferative, an angiogenesis inhibitor, or mixture thereof, in a nanoparticle form and a protein. Dependent claims 21-22 are directed to taxane.

US '331 is directed to a pharmaceutical formulation comprising taxane in a concentration of 30 mg to about 1000mg and dependent claim 24 further comprises albumin.

US '331 does not specify if the drug is in an amorphous form.

Westesen et al teach nanoparticles containing various poorly water-soluble drugs. See abstract. Westesen teaches the use of an amorphous form of the drug to provide for better solubility and bioavailability of poorly water-soluble drugs than utilizing a crystalline form. See column 5, lines 45-56. Generally amorphous forms of a substance exhibit a higher solubility and a faster dissolution than the crystals forms since they do not require lattice energy.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an amorphous drug form to arrive at the instantly claimed invention. One would have been motivated to do so since Westesen teaches the use of an amorphous form for better solubility and bioavailability of poorly water-soluble drugs and taxane are known to be poorly water-soluble drugs. Therefore, it is deemed an obvious modification to utilize an amorphous drug form of taxane.

It should be noted that the intended use (a composition for the treatment of hyperplasia) of the instant invention and the intended use of US '331 (a formulation for treatment of primary tumors) is not given patentable weight since it merely recites the purpose of the composition and does not provide a structural limitation.

Conclusion

All the claims are rejected at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sharmila S. Gollamudi
Examiner
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SSG

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